REMARKS

Applicants have amended the title of the specification, the headings within the specification, and the claims in order to place the application in condition for allowance. Applicants have reviewed the outstanding Official Action and thank the Examiner for her comments on amending the headings in the specification and these amendments have been made as requested.

Claim 14 is clarified to avoid ambiguous language and the wording of claim dependencies is placed in preferred form. Claim 16 is clarified by removing "(e.g. monodisperse)" into new claim 28 and claim 20 has been amended to refer back to method claim 14. Claim 26 is amended to more accurately reflect the contribution of the present invention and claim 27 deleted as redundant over this amendment.

With regard to the restriction requirement, the Office Action considers Applicant's response in section 1 and indicated that the combination of specific-sized binding particles with the turbidimetry cannot be a unifying feature because the particles (without reference to turbidimetry) are not considered to be a contribution over the known art. As a result, the Official Action has raised a unity objection on page 2 of the Official Action and claims 20-24 have not been examined.

Although these claims have been withdrawn from examination, Applicant reserves the right to re-join these claims when allowable subject matter is found, and to that end the first line of claim 20 has been amended to read "A kit for use as a diagnostic assay according to claim 14..." Since this claim incorporates all restrictions of the independent claim, Applicant believes that it is suitable for rejoinder when an allowable main claim is established.

Applicant has amended the title of the specification in order to be more descriptive as requested in the Official Action. Applicant has also amended the specification to include title headings in compliance with 37 C.F.R 1.77(b).

The Official Action also objects to claim 14 on the grounds of lack of clarity with

regard to the use of the singular and plural forms of "nanoparticle". Applicants believe that it is clear from the specification at page 15, line 34 to page 16, line 3 that a plurality of nanoparticles is intended to be used in the practice of the invention. In the amended claims, part (b) of claim 14 is amended to read 'Contacting said sample of said body fluid with anti-calprotectin antibodies or antibody fragments, to bind said calprotectin, wherein said anti-calprotectin antibodies or antibody fragments are immobilized by binding or coupling, either directly or indirectly, to nanoparticles to form antibody or antibody fragment coated nanoparticles; and.' Applicant believes that this is based clearly upon the original disclosure and renders the claim language entirely unambiguous.

Applicant notes that the preferred language proposed by the Examiner has been incorporated into the amended claims.

Applicant also notes that the term "monodisperse" is deleted from the amended claim 16 and is places in new dependent claim 28.

The Official Action rejects claims 26 and 27 as lacking enablement on the basis that a true diagnostic test must allow unambiguous diagnosis of each individual condition on the basis of a statistically significant difference in a particular parameter. The Applicant accepts that the use of calprotectin as the sole indicator in diagnosing the specified conditions was not the teaching of the application, and notes that the methods of diagnosis as originally claimed merely "comprises" the calprotectin determining steps recited. The measurement of calprotectin in isolation was not intended to provide a diagnostic result without additional factors being taken into account, as indicated by this open wording. In order to clarify the situation with regard to the value of calprotectin in diagnosis, claim 26 has been amended to read "A method for assessing the potential for or propensity to cardiovascular disease" this reflects the original disclosure of the application as filed (e.g. final paragraph of page 1). Claim 27 is deleted as redundant.

The term "in the range" is deleted from enclosed claim 14. Applicant believes that this addresses the Examiner's clarity objection.

The Official Action rejects claims 26-27 as lacking an essential step in which a

disease is diagnosed. As noted earlier, claim 26 is now amended to more accurately reflect the contribution of the inventors in reciting "A method for assessing the potential for or propensity to cardiovascular disease." Thus a step of diagnosing a disease is now not appropriate. Nonetheless, the step of correlating a calprotectin concentration above the threshold value with an indication of potential for or propensity to cardiovascular disease is included. This is based upon pages 10 and 11, particularly page 10, lines 30 to 32 and page 11, lines 18 to 28. Accordingly, it is most respectfully requested that this rejection be withdrawn. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record.

The rejection of claims 14-19 and 26 and 27 under 35 USC 103(a) as obvious over Arvesen et al in Craig has been carefully considered but is most respectfully traversed in view of the amendment to the claims and the following comments. The Official Action asserts the Arvesen et al teaches calprotectin as a marker in the context of cardiovascular disease. Actually, this is referred to in acute coronary Syndrome. However, the Examiner accepts that this citation does not teach the detection of calprotectin using the bead-based method claimed. To address this shortcoming, the Official Action cites Craig et al and indicates that the combination of Arvesen with that of Craig et al renders current claim 14 obvious. The Official Action argues that Craig teaches turbidimetric assessment using nanoparticles of diameter 30-100 nm bound to an antibody against the compound on interest.

There are at least two key issues which distinguish the present claims for the disclosures of the prior art, and neither of these aspects are taught towards or suggested in the cited documents. Firstly, the prior art makes no disclosure of calprotectin as a marker for the potential for Cardiovascular disease or propensity to Cardiovascular disease. Arvesen relates to patients with pre-existing conditions and it was known at the time of the invention that calprotectin was elevated in those who had suffered a serious cardiovascular event. Calprotectin is, however, a general inflammatory marker and a Cardiovasular even is certain to generate a major

inflammatory reaction. There was no teaching prior to the present application that would suggest calprotectin as a predictor of Cardiovascular disease status, as required by claims 26 and 27.

The second key issue relates to the calprotectin assay methods claims, and in particular to the difficulty of calprotectin as an analyte. On page 10 of the application as filed, the concentration of calprotectin in healthy subjects of low Cardiovasular disease potential is considered. This may be as low as 0.05 mg/L. This means that an assay for calprotectin which is to be clinically useful in the present invention must be able to distinguish calprotectin which is to be clinically useful in the present invention must be able to distinguish calprotectin levels a little above and a little below 0.3 mg/L (around 8 nM at a MW of 36.5 kDa). This is a remarkably low concentration, and places very exacting demands upon the sensitivity and accuracy of such an assay.

The method of Craig, although a turbidimetric assay, is a competitive method in which an analogue of the compound of interest is added to generate a turbid solution (part (1) of claim 1). When a sample containing a compound of interest is added (solution (2) of claim 1), this compound competes with the analogue and thus decreases the turbidity formation. Although effective for certain analytes, this method requires a relatively high concentration of the analyte of interest in order to generate an accurate signal. In particular, where only a low analyte concentration is present, the method results in the need for subtracting one large signal from another to generate a small difference. This is well known to be a highly error-prone practice, and where possible all scientific methods aim to avoid such a requirement. As a result of this, the method of Craig is not suitable for the assay of calprotectin at relevant concentrations, and if it were used then the result would not be sufficiently reliable for any useful clinical information to be gathered.

In contrast to the method of Craig, the method of the present invention is not a competitive assay method (there is no calprotectin analogue used) and rather than the calprotectin in the sample inhibiting the generation of turbidity, the analyte of interest is responsible for generating the turbidity. As a result, there is no requirement to subtract

two large signals in order to generate a value and thus the necessary sensitivity and accuracy are possible. It can be seen from each of the first five examples of the application as filed that no calprotectin analogue is used and thus the "increase in Igith absorption" described is directly due to the calprotectin causing the antibody-coated particles to come together.

The method of Craig teaches a competitive assay which is not highly suitable for calprotectin. As a result, the skilled worker, knowing of the very low calprotectin concentration in relevant samples would have no reasonable expectation that this method could be successful with calprotectin. Furthermore, even if the method of Craig was applied to calprotectin, the result would be a competitive assay in which the analyte suppresses the generation of turbidity, rather than a method of the present invention in which the analyte generates the turbidity. In view of both of these factors, it cannot be obvious to generate a method of the present invention by reference to Craig. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,

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